



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/769,579

01/30/2004

James W. Schumm

016026-9238

2176

23510 7590 03/19/2008
MICHAEL BEST & FRIEDRICH LLP
ONE SOUTH PINCKNEY STREET
P O BOX 1806
MADISON, WI 53701

EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT

PAPER NUMBER

1634

MAIL DATE

DELIVERY MODE

03/19/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/769,579	Applicant(s) SCHUMM ET AL.	
	Examiner JEANINE A. GOLDBERG	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 December 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-24 is/are pending in the application.
- 4a) Of the above claim(s) 23 and 24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21 and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to the papers filed December 13, 2007. Currently, claims 21-24 are pending. Claims 22-23 have been withdrawn as drawn to non-elected subject matter.
2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 13, 2007 has been entered.
3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
4. Any objections and rejections not reiterated below are hereby withdrawn.

Election/Restrictions

5. Applicant's election without traverse of HUMCSF1PO; HUMTPOX and HUMVWFA31 in the paper filed May 18, 2006 is acknowledged.

Claims 22-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Priority

6. This application claims priority to several US applications.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 21, 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caskey (5,364,759) in view of GenBank STR loci HUMTPOX, HUMVWFA31 and HUMCSF1PO and further in view of Fregeau (BioTechniques, Vol. 15, No. 1, pages

100-119, 1993) or Kimpton (PCR Methods and Applications, Vol. 3, pages 13-22, 1993) or Urquhart (Int. J. Leg. Med, Vol. 107, pages 13-20, August 1994).

Caskey discloses the claimed method that includes obtaining a DNA sample, amplifying STR sequences from the DNA sample, and evaluating the amplification products for identification (col. 7, lines 4-10). Caskey describes a preferred Caskey discloses the claimed method that includes obtaining a DNA sample, amplifying STR sequences from the DNA sample, and evaluating the amplification products for identification (col. 7, lines 4-10). Caskey teaches a definition of “multiplex polymerase chain reaction (mPCR)” (col. 6, lines 34-68). Further, Caskey teaches that mPCR includes a) primers composed of similar GC base compositions and lengths, b) longer extensions times up to 8 fold the normally utilized times and c) minimization of the number of PCR cycles performed to achieve detection. Caskey teaches that mPCR reaction is optimized for each reaction (col. 6, lines 65-66). Caskey identifies STR loci by searching all human sequences in GenBank (Example 1, col. 8). Strategies to determine the sequences flanking STRs are disclosed in Example 3 (col. 10). Although Caskey teaches that in a reaction with HUMARA and HUMFABP alleles appear as widely spaced doublets such that adjacent alleles overlap, different label may be applied to the different loci to unambiguously identify the alleles (col. 18). Caskey teaches the primers of SEQ ID NO: 15, 16, 19, 20, 27, and 28 as primers for the amplification of HUMFABP, HUMPRTB, and HUMTH01, respectively. As described in Example 7, the comparison of amplified alleles by polyacrylamide gel electrophoresis and visualization of the DNA by fluorescent analysis. STR markers can be detected with

Art Unit: 1634

non-denaturing and denaturing electrophoretic systems. Silver staining detection methods are all applicable. Additionally, the loci are selected so that the amplification products of the alleles from different loci do not overlap. Further, Caskey teaches that the source of DNA to be tested can be any medical or forensic sample and can include blood, semen, vaginal swabs, tissue, hair, saliva, urine and mixtures of body fluids (col. 6, para. 2). Caskey discloses the use of allelic ladders as internal standards (col. 7, lines 15-19, and col. 19, lines 15-18). Additionally, Caskey teaches kits which contain a container having oligonucleotide primer pair for amplifying STRs and optionally, standards (col. 8 and col. 21, Example 10). Rather than citing STR containing loci, Caskey refers to STR sequences by their alphabetical designation as indicated in Table I. Additionally, Caskey does not recite locus combinations in examples 4-7 and tables 6-9, where data from multiplex amplification of said alleles is performed and analyzed. Caskey describes the level of skill of an ordinary artisan by stating that once STR sequences and their flanking sequences are obtained, primer pairs may be designed and synthesized according to the flanking sequences and PCR amplification and comparison of amplified products may be performed to detect the short tandem repeats (col. 4, lines 9-17, col. 5, lines 16-53, col. 6, lines 58-60). Identical primers were used in the instant application for HUMFABP, HUMTH01, and HUMPTB. Therefore, the method by which Caskey derives primers for STR loci appears to be consistent with the method of the instant application. Caskey also comments on the empirical nature of multiplex amplification reactions and points out that each reaction must be optimized (col. 6, line 65).

Caskey does not specifically teach the recited locus combinations.

However, the STR loci HUMTPOX, HUMVWFA31 HUMTH01 and HUMCSF1PO have been taught by GenBank Accession No: M68651, M25858, D00269 and X14720.

Fregeau teaches DNA typing with fluorescently tagged STRs for a sensitive and accurate approach to human identification. Fregeau teaches a multiplex system which contains HUMCD4, HUMFABP, and HUMCATBP2 (pg. 114, col. 3)(limitations of Claim 21, 48-54). DNA for the multiplex was extracted from blood, hair roots, dried bloodstains (pg. 101, col. 3, para. 1). Fregeau demonstrates that primers for STR systems HUMHPRT, HUMTH01, HUARA, HUMCD4, HUMFABP, HUMPLA2A1 and HUMRENA4 were used to amplify genomic DNA (pg. 102, col. 1, and Table 1). Fregeau teaches primers identical to the primers of SEQ ID NO: 1, 2, 9, 15, 16, 19, 20, 27, 28, and 30 (Table 1). Fregeau teaches HUMvWF, HumFABP, HumACTBP2 and D21S11 all have the same annealing temperature of 64 to 65 degrees and have shown to permit multiplex amplification which saves in reagents and sample template (pg. 117, col. 3, para 2). Further, HumCD4, HumARA, HumTHO01 have the same optimal annealing temperature, 68 degrees. The STR alleles were then separated and detected on a denaturing polyacrlamide gel electrophoresis (pg. 106). The fluorescent amplification products were resolved on polyacrylamide gels with various gel parameters varied (pg. 103, col. 1). A comparison was made between allele sized from silver-stained polyacrylamide gels and automated fluorescent analysis (pg. 110, col. 3). A four STR system, HUMCD4, HUMHPRT, HUMTH01, HumARA, was explored using additional amplification cycles. Fregeau describes multiplex amplification of polymorphic STR

Art Unit: 1634

sequences of loci including HUMHPRTB, HUMTH01, HUMCD4, HUMFABP and HUMPLA2A (pg. 117, col. 3, para. 2). Empirical evaluation, a specific annealing temperature for each of the STR systems was found to generate consistent allelic profiles with high specificity and sensitivity after 28 cycles of amplification (pg. 115, col. 1). Several benefits of STRs analysis was elucidated including minimal only amounts of template DNA need to be used, the STR alleles can be resolved on sequencing gels using radiolabeled primers or having been processed with cold primers and detected after silver staining, and STRs are amenable to automation (pg. 100-101). Further, Fregeau teaches that careful selection of a refined polyacrylamide gel system and appropriate STR loci that have allele size ranges that are mutually resolvable should allow for additional systems to be analyzed with the same fluorescent tag (pg. 117, col. 3). Fregeau specifically teaches that multiplex amplification represents a savings in reagents and sample template.

Kimpton describes the multiplex amplification of polymorphic STR sequences of loci including HUMVWA31, HUMTH01, HUMF13A1, HUMFESFPS, HUMCD4, HUMDHER, HUMCYARO3, HUMAPOAII, HUMPLA2A, HUMIIDA, HUMFABP, HUMGABGA, HUMACTBP2 and D21S11. In Kimpton the combinations of loci are not identical to the combinations claimed. However, Kimpton performs multiplex amplification of STR containing loci in combinations of two, three, four, and seven, chosen loci from HUMVWA31, HUMTH01, HUMF13A1, HUMFESFPS, HUMCD4, HUMDHER, HUMCYARO3, HUMAPOAII, HUMPLA2A, HUMIIDA, HUMFABP, HUMGABGA, HUMACTBP2 and D21S11. Kimpton teaches primers for the amplification

Art Unit: 1634

of HUMACTBP2, HMAPOAII, HUMFABP, HUMTH01, HUMvWA31/A which are identical to the primers taught in the instant application, namely SEQ ID NO: 1, 4, 15, 27, and 32. Kimpton teaches the PCR component concentrations and cycling parameters were optimized for each loci individually. The STRs suitable for co-amplification (multiplexing) were then selected on the basis of similar optimal reaction conditions and compatible allele size ranges (pg. 16, col. 1). Efficient amplification of all loci in multiplex systems was achieved by the adjustment of annealing temperature and individual primer concentration (pg. 19, col. 3). Further, STR loci with overlapping allele size ranges were differentiated by use of different fluorescent dye labels (pg. 16, col. 1).

Urquhart teaches a method of simultaneously determining the alleles present in at least two STR loci. Urquhart teaches a method of preparing DNA from whole blood and performing a PCR amplification using genomic DNA. Each of two primers for each locus were added to the mixture and PCR was performed. The PCR products were electrophoresed in agarose gels, purified and sequenced (pg. 14, col. 1-2). Urquhart teaches primers which are identical to SEQ ID NO: 10, 15, 27, and 32 (Table 1) that correspond to HUMVWFA31 and HUMTHO1. Urquhart also teaches primers which are very homologous to SEQ ID NO: 11, 16, 25, 26 and 31. The alleles were evaluated by separating sizing alleles with an allelic ladder (pg. 14, col. 1). Further, Urquhart teaches markers used in the quadruplex STR system were labeled fluorescently (pg. 13-14). The DNA obtained was prepared from blood (pg. 14, col. 1). The conditions for the reaction were optimized in respect to the different STR's incorporated into the reaction (pg. 14, col. 2). The primers used in the study were all derived from the published or

Art Unit: 1634

GenBank sequences (pg. 14, col. 1). Although Urquhart does not specifically teach **all** of the recited combinations disclosed in the instant application, Urquhart, does teach the amplification of HUMVWFA31, HUMTH01, HUMF13A01, HUMFES/FPS, HUMCD4, HUMPLA2A1, HUMFOLP23, HUMCYAR04, HUMTFIIDA, HUMFABP, HUMGABRB15, and HUMD21S11 (pg. 14, col. 2). Urquhart teaches that the annealing temperature for HUMTH01, HUMCD4, HUMPLA2A1, HUMFOLP23, HUMCYAR04, HUMTFIIDA, HUMFAB, HUMGABRB15 and HUMD21S11 are all 60 degrees (pg. 14, col. 2).

Therefore, to one of ordinary skill in the art at the time the invention was made, it would have been **prima facie** obvious to use any number of primers, including SEQ ID NO: 1-32, among other possible sequences that could accomplish the same goal for the process of simultaneously amplifying specified loci which provide a different pattern and thus a means of confirmation or subsequent analysis. SEQ ID NO:s 1-14, 17-18, 21-26, 29-32 are not specifically taught by Caskey as specific primers for the respective STR loci. The claimed primers, however, would have been obvious based on the teaching of Caskey about primer design and synthesis and the known sequences of the claimed loci, which were available from GenBank. Additionally, Caskey was able to perform multiplex amplification of HUMTH01 in combination with other loci, which reiterates the level of skill in the art. As admitted in the specification, "successful combinations are generated by trial and error (routine experimentation) of locus combinations and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified"(pg. 10, lines 10-13). Therefore, the claimed invention would have been obvious over Caskey in view of the GenBank entries.

Response to Arguments

The response traversed the rejection. The response asserts that the claims are directed to methods employing specific combinations of loci that can be simultaneously determined in a multiplex reaction to determine the alleles present in those loci. The response asserts that there is no teaching suggestion or motivation to modify the references to make the claimed invention. This argument has been reviewed but is not persuasive. This argument has been thoroughly reviewed but is not deemed persuasive because KSR forecloses the argument that an explicit specific teaching, suggestion or motivation in the references is required to support a finding of obviousness. The response admits on the record that one skilled in the art may have been interested in identifying sets of loci that could be co-amplified but states that none of the references provide any teaching, suggestion or motivation to make the particular combinations of loci (see page 3 of response filed December 13, 2007).

The response states that the very large number of possible combinations of at least three loci that could be made using the 168 trinucleotide and tetranucleotide repeats known in the art at the time the invention was made does not provide motivation to modify the prior art to arrive at the method of employing a particular combination. This argument has been reviewed but is not persuasive. KSR specifically states that “when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and

Art Unit: 1634

common sense.” Here, there are a finite number of loci taught in the art at the time the invention was made. The art clearly teaches the co-amplification of many various combinations of STR loci which suggests that the claimed combinations were predictable as possible solutions. The art further discusses various routine optimization that may be required to obtain a successful result. Obviousness does not require absolute predictability of success. The ordinary artisan thus, would have clearly recognized the ability to place these three loci into a co-amplification assay with predictability.

The response asserts that the examiner has not indicated a reason why one of skill in the art would specifically select the loci in the manner claimed. This argument has been reviewed but not persuasive. The rejection is made on the basis of obvious to try. It would have been obvious that a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103. Thus, the basis for the rejection under 103 has been indicated.

The response asserts that there is no reasonable expectation of success. The response asserts that although Caskey teaches choosing primers for use in multiplex analysis and the specification states, “successful combinations are generated by trial and error (routine experimentation) of locus combinations and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified”(pg.

Art Unit: 1634

10, lines 10-13), the reasonable expectation of success must be found in the prior art and not in applicant's disclosure. This argument has been reviewed but is not convincing. The art, namely Kimpton, Fregeau and Urquhart specifically teach the routine nature of designing multiplex amplification of short tandem repeat loci. Kimpton, 1993, specifically teaches that microsatellite loci were found to co-amplify with relative ease (page 16). Moreover, Kimpton teaches that the STR loci studies were shown to coamplify readily under standard PCR conditions. And efficient amplification of all loci in multiplex systems was achieved by the adjustment of annealing temperature and individual primer concentration (page 19). The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to co-amplify STR loci. The reasonable expectation of success is based not on applicants disclosure, but on the vast teachings in the art. However, the specification, itself, suggests that the combinations, as provided in the instant claims, were a product of trial and error experimentation.

The declaration by Cynthia Sprecher, an inventor, has been received and carefully reviewed. As previously noted that "Although an affidavit or declaration which states only conclusions may have some probative value, such an affidavit or declaration may have little weight when considered in light of all the evidence of record in the application. In re Brandstadter, 484 F.2d 1395, 179 USPQ 286 (CCPA 1973)." In the instant case, an opinion declaration from an interested party will have little weight when considered in light of the evidence of the skill in the art at the time the invention was

Art Unit: 1634

made. The response asserts that the declaration of Dr. Sprecher is not only opinion testimony but also contains statements of facts.

The declaration of Dr. Sprecher states that "I am of the opinion that it would not have been obvious to one having ordinary skill in the art, at the time the application to which the present application claims priority was filed, to combine the disclosures of the cited references in order to result in the subject matter of the rejected claims" (page 2, para 4). This appears to be directed solely to the ultimate legal conclusion. Thus, this argument is not persuasive.

The declaration further discusses the teachings of Casky and Schumm and Kimpton and Urquhart (see page 3, para 5-6). The declaration then states that it was well-established that there was an advantage of having additional loci and differing sets of loci (page 3, para 7). However the declarant states that the selection of loci was not a trivial manner and required inventive skill. The declarant states that "in my experience,...selecting STR loci for DNA typing, and subsequently co-amplifying the selected STR loci in a multiplex reaction, was very laborious and unpredictable" (page 3-4). Further, Dr. Sprecher teaches that it was not predictable and would require extensive trial and error. This argument has been reviewed but is not persuasive. To determine whether something is predictable is not merely the quantity or amount of work. The test is not merely quantitative, since a considerable amount of experimentation is permissible, it is merely routine. Thus, merely because the method is very laborious does not suggest that the method is unpredictable. As noted above, "Obviousness does not require absolute predictability of success." In re O 'Farrell, 853

Art Unit: 1634

F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful. Thus, as here, the prior art teaches an enabling methodology to perform multiplexing of STR loci, suggests to modify the references to encompass additional multiplex loci and suggests alternative combinations would be successful.

The response asserts that Caskey provides no teaching as to which loci could be amplified to produce results that could be evaluated in any meaningful way because of the overlapping alleles. This argument has been reviewed but is not convincing because Caskey provides methods for choosing primers for use in multiplex analysis. Further the specification, "successful combinations are generated by trial and error (routine experimentation) of locus combinations and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified"(pg. 10, lines 10-13).

The response asserts that the references indicate that the selection of STR loci that can be co-amplified is not a trivial matter, but rather one that would require a considerable amount of experimentation. This argument has been reviewed but is not convincing because the standard for obvious is not absolute expectation of success, but rather reasonable expectation of success. Given the teachings of the references there is a reasonable expectation of success. While some routine experimentation and optimization may be required to determine the exact parameters which allow successful

Art Unit: 1634

optimization of the assay, this routine optimization is not an indice of non-obviousness.

As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the probe selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the unexpected results must be supported by evidence, not argument.

Thus for the reasons above and those already of record, the rejection is maintained.

9. Claims 21, 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schumm et al. (US Pat. 5,783,406, July 21, 1998) in view of Fregeau (BioTechniques,

Art Unit: 1634

Vol. 15, No. 1, pages 100-119, 1993) or Kimpton (PCR Methods and Applications, Vol. 3, pages 13-22, 1993) or Urquhart (Int. J. Leg. Med, Vol. 107, pages 13-20, August 1994).

Schumm teaches an assay for detecting at least one short tandem repeat sequence from DNA at a specific locus using an allelic ladder containing at least two short tandem repeat sequences. Schumm teaches allelic ladders for evaluating short tandem repeat sequences at a specific locus wherein the locus is selected from the group consisting of: HUMCD4, HUMCSF1PO, HUMCYP19 (CYARP450), HUMF13A01, HUMF13B, HUMFESFPS, HUMLPL (LIPOL), HUMPLA2A1 (PLA-AZ), HUMTPOX and HUMVWFA31. Schumm further teaches a multiplex method for analyzing HUMCSF1PO, HUMFESFPS, and HUMTH01 simultaneously. Schumm further teaches primers applicable for each of the STR.

Schumm does not specifically teach a multiplex method for analyzing HUMTPOX, HUMCSF1PO and HUMVWFA31.

However, Fregeau teaches DNA typing with fluorescently tagged STRs for a sensitive and accurate approach to human identification. Fregeau teaches a multiplex system which contains HUMCD4, HUMFABP, and HUMCATBP2 (pg. 114, col. 3)(limitations of Claim 21, 48-54). DNA for the multiplex was extracted from blood, hair roots, dried bloodstains (pg. 101, col. 3, para. 1). Fregeau demonstrates that primers for STR systems HUMHPRT, HUMTH01, HUARA, HUMCD4, HUMFABP, HUMPLA2A1 and HUMRENA4 were used to amplify genomic DNA (pg. 102, col. 1, and Table 1). Fregeau teaches primers identical to the primers of SEQ ID NO: 1, 2, 9, 15, 16, 19, 20,

Art Unit: 1634

27, 28, and 30 (Table 1). Fregeau teaches HUMvWF, HumFABP, HumACTBP2 and D21S11 all have the same annealing temperature of 64 to 65 degrees and have shown to permit multiplex amplification which saves in reagents and sample template (pg. 117, col. 3, para 2). Further, HumCD4, HumARA, HumTHO01 have the same optimal annealing temperature, 68 degrees. The STR alleles were then separated and detected on a denaturing polyacrlamide gel electrophoresis (pg. 106). The fluorescent amplification products were resolved on polyacrylamide gels with various gel parameters varied (pg. 103, col. 1). A comparison was made between allele sized from silver-stained polyacrylamide gels and automated fluorescent analysis (pg. 110, col. 3). A four STR system, HUMCD4, HUMHPRT, HUMTH01, HumARA, was explored using additional amplification cycles. Fregeau describes multiplex amplification of polymorphic STR sequences of loci including HUMHPRTB, HUMTH01, HUMCD4, HUMFABP and HUMPLA2A (pg. 117, col. 3, para. 2). Empirical evaluation, a specific annealing temperature for each of the STR systems was found to generate consistent allelic profiles with high specificity and sensitivity after 28 cycles of amplification (pg. 115, col. 1). Several benefits of STRs analysis was elucidated including minimal only amounts of template DNA need to be used, the STR alleles can be resolved on sequencing gels using radiolabeled primers or having been processed with cold primers and detected after silver staining, and STRs are amenable to automation (pg. 100-101). Further, Fregeau teaches that careful selection of a refined polyacrylamide gel system and appropriate STR loci that have allele size ranges that are mutually resolvable

Art Unit: 1634

should allow for additional systems to be analyzed with the same fluorescent tag (pg. 117, col. 3).

Kimpton describes the multiplex amplification of polymorphic STR sequences of loci including HUMVWA31, HUMTH01, HUMF13A1, HUMFESFPS, HUMCD4, HUMDHER, HUMCYARO3, HUMAPOAII, HUMPLA2A, HUMIIDA, HUMFABP, HUMGABGA, HUMACTBP2 and D21S11. In Kimpton the combinations of loci are not identical to the combinations claimed. However, Kimpton performs multiplex amplification of STR containing loci in combinations of two, three, four, and seven, chosen loci from HUMVWA31, HUMTH01, HUMF13A1, HUMFESFPS, HUMCD4, HUMDHER, HUMCYARO3, HUMAPOAII, HUMPLA2A, HUMIIDA, HUMFABP, HUMGABGA, HUMACTBP2 and D21S11. Kimpton teaches primers for the amplification of HUMACTBP2, HUMAPOAII, HUMFABP, HUMTH01, HUMvWA31/A which are identical to the primers taught in the instant application, namely SEQ ID NO: 1, 4, 15, 27, and 32. Kimpton teaches the PCR component concentrations and cycling parameters were optimized for each loci individually. The STRs suitable for co-amplification (multiplexing) were then selected on the basis of similar optimal reaction conditions and compatible allele size ranges (pg. 16, col. 1). Efficient amplification of all loci in multiplex systems was achieved by the adjustment of annealing temperature and individual primer concentration (pg. 19, col. 3). Further, STR loci with overlapping allele size ranges were differentiated by use of different fluorescent dye labels (pg. 16, col. 1).

Urquhart teaches a method of simultaneously determining the alleles present in at least two STR loci. Urquhart teaches a method of preparing DNA from whole blood

Art Unit: 1634

and performing a PCR amplification using genomic DNA. Each of two primers for each locus were added to the mixture and PCR was performed. The PCR products were electrophoresed in agarose gels, purified and sequenced (pg. 14, col. 1-2). Urquhart teaches primers which are identical to SEQ ID NO: 10, 15, 27, and 32 (Table 1).

Urquhart also teaches primers which are very homologous to SEQ ID NO: 11, 16, 25, 26 and 31. The alleles were evaluated by separating sizing alleles with an allelic ladder (pg. 14, col. 1). Further, Urquhart teaches markers used in the quadruplex STR system were labeled fluorescently (pg. 13-14). The DNA obtained was prepared from blood (pg. 14, col. 1). The conditions for the reaction were optimized in respect to the different STR's incorporated into the reaction (pg. 14, col. 2). The primers used in the study were all derived from the published or GenBank sequences (pg. 14, col. 1). Although Urquhart does not specifically teach **all** of the recited combinations disclosed in the instant application, Urquhart, does teach the amplification of HUMVWFA31, HUMTH01, HUMF13A01, HUMFES/FPS, HUMCD4, HUMPLA2A1, HUMFOLP23, HUMCYAR04, HUMTFIIDA, HUMFABP, HUMGABRB15, and HUMD21S11 (pg. 14, col. 2). Urquhart teaches that the annealing temperature for HUMTH01, HUMCD4, HUMPLA2A1, HUMFOLP23, HUMCYAR04, HUMTFIIDA, HUMFAB, HUMGABRB15 and HUMD21S11 are all 60 degrees (pg. 14, col. 2).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to have modified the teachings of Schumm with the loci of Fregeau, Kimpton or Urquhart to obtain the claimed invention because the skilled artisan would have been motivated by the teachings of Fregeau,

Art Unit: 1634

Kimpton, or Urquhart to choose any reasonable number of known STR containing loci, and use them in desired combinations for detection and analysis of polymorphisms in STR loci. Further, it would have been obvious to have chosen any number of known STR containing loci which can be co-amplified together including those suggested by Schumm and use them in desired combinations for detection and analysis of polymorphisms in STR loci, because such a co-amplification was in fact performed by Kimpton, Fregeau and Urquhart. Both Kimpton (Int. J. Leg. Med), Fregeau, Kimpton and Urquhart teach intricate details of multiplex PCR reactions, such as critical parameters for primer design, optimization of cycling conditions, and pros and cons of gel electrophoresis, and visualization techniques (silver stain vs. fluorescence). Both Kimpton and Fregeau references comment on the empirical nature of selecting primers and amplification conditions to achieve an appropriate multiplex amplification system. Kimpton teaches "STRs suitable for co-amplification were selected on the basis of similar optimal reaction conditions and compatible allele size ranges" (pg. 16, col. 1, para 3). For example, Fregeau teaches, HUMTH01 and HUMCD4 both have annealing temperatures of 68 degrees, and have different allele size (bp) which do not overlap (Table 1 and Table 3). Similarly, ACTBP2 and HUMFABP both have annealing temperatures of 64 degrees and do not have overlapping allele sizes (Table 1 and Table 3). Therefore the at least two STR loci would contain clearly distinguishable STR allelic profiles (pg. 115, col. 3) and would have been obvious to combine the two STR loci to obtain the claimed invention. The choice of STR loci chosen to multiplex is dependent on what information is desired from the allele analysis. As exemplified in the

Art Unit: 1634

art, gel analysis of several STR loci on the same gel saved time and reagents. One of ordinary skill in the art would have been motivated to design appropriate primers and optimize PCR conditions in order to co-amplify additional combinations of STR loci for the benefit of saving time, reagents and other supplies in the amplification process as taught by Fregeau (pg. 117). It is also evident from these references that the loci were chosen for their already demonstrated polymorphic properties and that implementation of multiplex amplification of combinations thereof was easily achieved by routine optimization of the well known PCR methodology adapted for multiplex purposes. As admitted in the specification, "successful combinations are generated by trial and error (routine experimentation) of locus combinations and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified"(pg. 10, lines 10-13). Thus, the claimed invention would have been obvious over Schumm in view of Fregeau, Kimpton or Urquhart. Schumm specifically provides the primer pairs for each of the STR loci. The ordinary artisan would have been motivated to expand the assay to the other loci taught by Schumm to enable further analysis and distinguishment of alleles, as taught by Schumm.

Response to Arguments

The response traverses the rejection. The response asserts that the rationale for the rejections appear to be substantially the same. Thus, the response to arguments above are incorporated herein.

The response asserts that the references indicate that the selection of STR loci that can be co-amplified is not a trivial matter, but rather one that would require a

Art Unit: 1634

considerable amount of experimentation. This argument has been reviewed but is not convincing because the standard for obvious is not absolute expectation of success, but rather reasonable expectation of success. Given the teachings of the references there is a reasonable expectation of success. While some routine experimentation and optimization may be required to determine the exact parameters which allow successful optimization of the assay, this routine optimization is not an indice of non-obviousness. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the probe selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the inoperability of the prior art must be supported by evidence, not argument.

The response asserts that Schumm does not suggest any of the specifically claimed combinations. This argument has been reviewed but is not persuasive. The claim would have been obvious because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Here, Schumm teaches allelic ladders for evaluating short tandem repeat sequences at a specific locus wherein the locus is selected from the group consisting of: HUMCD4, HUMCSF1PO, HUMCYP19 (CYARP450), HUMF13A01, HUMF13B, HUMFESFPS, HUMLPL (LIPOL), HUMPLA2A1 (PLA-AZ), HUMTPOX and HUMVWFA31. Schumm further teaches a multiplex method for analyzing HUMCSF1PO, HUMFESFPS, and HUMTH01 simultaneously. Schumm further teaches primers applicable for each of the STR. Schumm teaches a finite number of loci for multiplexing. Fregeau, Urquhart and Kimpton clearly teach the parameters known in the art for multiplexing loci. Both Kimpton (Int. J. Leg. Med), Fregeau, Kimpton and Urquhart teach intricate details of multiplex PCR reactions, such as critical parameters for primer design, optimization of cycling conditions, and pros and cons of gel electrophoresis, and visualization techniques (silver stain vs. fluorescence). Both Kimpton and Fregeau references comment on the empirical nature of selecting primers and amplification conditions to achieve an appropriate multiplex amplification system. Kimpton teaches "STRs suitable for co-amplification were selected on the basis of similar optimal reaction conditions and compatible allele size ranges" (pg. 16, col. 1, para 3). Thus, there would have been a reasonable expectation of success to select

Art Unit: 1634

the claimed loci and design a multiplex method given the guidance in the art. Moreover, the evidence of record illustrates that the experimentation performed was routine at the time the invention was made. As admitted in the specification, "successful combinations are generated by trial and error (routine experimentation) of locus combinations and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified"(pg. 10, lines 10-13).

The response asserts that Schumm does not provide a suggestion or motivation to combine its disclosure with those of Freageau, Kimpton and/or Urquhart. This argument has been thoroughly reviewed but is not deemed persuasive because KSR forecloses the argument that an explicit specific teaching, suggestion or motivation in the references is required to support a finding of obviousness.

Schumm specifically teaches using the particular markers from within a group of 10 STR markers. Thus, selection of at least three loci from within the group of 10 markers is certainly a finite number as discussed above with regard to the obvious to try analysis of KSR.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

10. No claims allowable over the art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Art Unit: 1634

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/

Primary Examiner

March 19, 2008